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Research Paper

TP53 gene rs1042522 allele G decreases neuroblastoma risk: a two-centre case-control study

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Abstract

The *TP53* gene plays a crucial role in the prevention of cancer formation, which is closely related to *TP53* mutation. *TP53* gene polymorphism rs1042522 C>G was largely investigated in various cancers, but its contribution to neuroblastoma is as yet undefined. Here, we evaluated the effect of the *TP53* gene rs1042522 C>G polymorphism on the development of neuroblastoma in two different regions, with patients from hospitals in both North and South China. The clinical data involved 374 patients and 812 controls. The resulting odds ratios (ORs) and 95% confidence intervals (CIs) were used with a logistic regression model to determine the intensity of associations between the factors of interest. We found that the *TP53* gene rs1042522 allele G was associated with a reduced risk of developing neuroblastoma. In our stratified analysis of age, sex, primary sites and clinical stages, we observed that male children, older than 18 months, with tumours derived from the mediastinum who had the rs1042522 CG/GG genotypes were at a decreased risk of developing neuroblastoma. These results indicate that the *TP53* gene rs1042522 allele G may be a potential protective factor against neuroblastoma in Chinese children.

Key words: neuroblastoma, TP53, polymorphism, susceptibility

Introduction

Neuroblastoma is the most common solid tumour in infants. According to statistics, after leukaemia and brain cancer, it has become the third most common cancer in children [1]. Approximately 15% of children around the world who died of cancer died as a result of neuroblastoma, and approximately 90% of cases occur in children less than 5 years old [2]. More than half of neuroblastoma patients are diagnosed as high-risk cases with poor prognoses. The current treatment of neuroblastoma is on the rise, and the prognosis for some children with low-risk neuroblastoma has been improved [2]; however, 15% of children with neuroblastoma die each year. Therefore, looking for more susceptibility genes is an urgent task.

Previous epidemiological studies have shown that there are familial susceptibility genes in the rare familial neuroblastoma [3]. However, in the sporadic cases, these familial susceptibility genes do not play a significant role [4]. Specifically, if parents are exposed to some dangerous environmental contaminant (radiation sources, carcinogens, etc.) before or during pregnancy, there is no evidence that the children of such parents are more likely to be affected by neuroblastoma than the children of unexposed parents. Growing evidence from genome-wide association studies (GWASs) indicate that genetic polymorphisms are implicated in neuroblastoma. For example, the study found that a low risk of neuroblastoma was associated with the genes *HSD17B12* and *DDX4* [5]. Highly enriched *CASC15*

and *BARD1*, *LMO1* polymorphisms have been found in children with high risk of developing neuroblastoma [6-8]. Moreover, candidate gene approaches also identified genetic associations in *NEFL* [9] and *CDKN1B* [10] genes with neuroblastoma susceptibility. These studies suggest that genetic polymorphisms may affect neuroblastoma formation in some way.

TP53 gene is located on the short arm of chromosome 17 and is 20 kb in humans. TP53 plays a role in the inhibition of apoptosis, genomic stability and angiogenesis and has many anti-cancer mechanisms [11]. Among the various SNPs in *TP53* gene, rs1042522 G>C is a hotspot polymorphism, which leads to the substitution of proline for arginine (Arg72Pro) at codon 72 of the p53 protein [12]. Multiple data analyses suggest that there are different degrees of association between rs1042522 G>C and susceptibility to cancers, including cervical cancer [13], prostate cancer [14], breast cancer [15], squamous cell carcinoma [16] and lung cancer [17]. However, the role of rs1042522 C>G on the risk of neuroblastoma remains un-fully elucidated.

In our previous experiments, we found that the *TP53* gene rs1042522 C>G polymorphism may be related to the occurrence of mediastinal neuroblastoma in children with neuroblastoma in South China [18]. To obtain more precise and reliable data on the association between *TP53* gene polymorphisms and neuroblastoma risk, we further conducted a more comprehensive case-controls study with participants from two hospitals in North and South China. The current study aims to provide new strategies and ideas for improving the diagnosis and treatment of neuroblastoma.

Materials and methods

Study subjects

This study involved two independent case-control populations. The first population was from Henan Province and consisted of 118 neuroblastoma patients and 281 controls [19]. The other population was from our previous study that was conducted in Guangdong Province [18, 20]. All of the children were diagnosed with neuroblastoma, with the diagnosis confirmed by more than two pathologists and their DNA was available for testing. They were all Chinese. All control subjects were free from serious underlying medical conditions and were recruited from the same hospital. Their DNA was also available. The major clinical and biological characteristics of the patient, including age, gender, sites of tumour origin, and the clinical stage of the neuroblastoma (International Neuroblastoma Staging System) were collected. The eligibility criterion for genome-wide genotyping was the ability to obtain 2.0 μg of high quality DNA from peripheral blood. The study was approved by the Institutional Review Committee of the First Affiliated Hospital of Zhengzhou University. The participants in this study gave informed written consent. The demographic characteristics of all participants are shown in **Supplemental Table 1**. There was no significant difference in age or gender between the case group and the control group in either region. The sites of neuroblastoma origin were also consistent: adrenal glands (135; 36.10%), retroperitoneal (109; 29.14%), mediastinal (87; 23.26%) and neuroblastomas in other regions (35; 9.36%). Among the samples, 8 sites of origin could not be determined (2.14%), and 69 (18.45%), 96 (25.67%), 63 (16.84%), 126 (33.69%) and 12 (3.21%) patients were classified as I, II, III, V and 4s, respectively, according to INSS criteria, with 8 cases (2.73%) classified as NA (not available) due to a lack of information.

SNP selection and genotyping

The SNP rs1042522 C>G in the *TP53* gene was chosen [18]. The genomic DNA was isolated from venous blood samples using the TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd., Beijing, China) according to manufacturer's instructions. Genotyping was performed by TaqMan real-time PCR as published previously [18, 19]. To ensure the accuracy of genotyping results, a randomly selected 10% of the samples were genotyped by the DNA sequencing method. The concordance rate for the quality control samples was 100%.

Statistical analysis

The goodness-of-fit χ^2 test was performed to assess if the selected SNP deviated from Hardy-Weinberg equilibrium among controls. The two-sided χ^2 test was used to compare demographic variables and genotype frequencies of the cases and controls. ORs and their corresponding 95% CIs were computed by unconditional logistic regression analyses with or without adjustment for age and gender. The SAS statistical package (version 9.1; SAS Institute, Cary, NC) was used to perform all statistical analyses. All reported *P* values were two sided, and a *P* value < 0.05 was considered statistically significant.

Results

TP53 gene rs1042522 C>G polymorphism and neuroblastoma risk

Table 1 shows the genotype frequencies, combination of *TP53* gene rs1042522 C>G polymorphism and the relationship with the risk of neuroblastoma in Henan and Guangdong Provinces.

Our observations agree with Hardy-Weinberg equilibrium conditions (P=0.919) among the combined controls, using good-of-fit χ^2 test. In Henan Province, the genotype frequency distribution of the *TP53* gene rs1042522 C>G polymorphism was 37.29% (CC), 49.15% (CG) and 13.56% (GG) in the patients and 29.54% (CC), 53.02% (CG) and 17.44% (GG) in the controls. In Guangdong Province, the distribution was 35.55% (CC), 42.19% (CG) and 22.27% (GG) in the patients and 29.25% (CC), 48.11% (CG) and 22.64% (GG) in the controls. In both provinces combined, the distribution was 36.10% (CC), 44.39% (CG) and 19.52% (GG) in the patients and 29.35% (CC), 49.82% (CG) and 20.84% (GG) in the controls. Looking at Henan Province and Guangdong Province individually, we found that rs1042522 C>G was not associated with the risk of neuroblastoma. However, when we further analysed the relationship between the *TP53* gene polymorphism and neuroblastoma risk by combining the study populations in Henan and Guangdong Provinces, we found that rs1042522G carriers were associated with a reduced risk of neuroblastoma (CG/GG vs. CC: adjusted odds ratios (OR) = 0.74, 95% confidence interval (CI) = 0.57-0.95, P = 0.020).

Stratification analysis

We further explored the association between the rs1042522 C>G polymorphism and neuroblastoma susceptibility by age, sex, tumour origins and clinical stages (**Table 2**). Compared with the CC genotype, the rs1042522 CG/GG genotypes were associated with a decreased risk of developing neuroblastoma at ages greater than 18 months (adjusted OR = 0.70, 95% CI = 0.51-0.96, P = 0.027), male (adjusted OR = 0.66, 95% CI = 0.47-0.92, P = 0.014) and for tumours originating from the mediastinum (adjusted OR = 0.57, 95% CI = 0.38-0.86, P = 0.007).

Table 1. Association between *TP53* rs1042522 C>G polymorphism and neuroblastoma susceptibility

Genotype	Cases n (%)	Controls n (%)	P [a]	Crude OR (95% CI)	P	Adjusted OR (95% CI) [b]	P [b]
Henan province							
CC	44 (37.29)	83 (29.54)		1.00		1.00	
CG	58 (49.15)	149 (53.02)		0.73 (0.46-1.18)	0.203	0.71 (0.44-1.15)	0.164
GG	16 (13.56)	49 (17.44)		0.62 (0.31-1.21)	0.158	0.60 (0.31-1.18)	0.140
Additive			0.276	0.77 (0.56-1.07)	0.118	0.76 (0.55-1.05)	0.099
Dominant	74 (62.71)	198 (70.46)	0.129	0.71 (0.45-1.11)	0.130	0.68 (0.43-1.08)	0.103
Recessive	102 (86.44)	232 (82.56)	0.338	0.74 (0.40-1.37)	0.340	0.74 (0.40-1.36)	0.334
Guangdong province							
CC	91 (35.55)	155 (29.25)		1.00		1.00	
CG	108 (42.19)	255 (48.11)		0.72 (0.51-1.02)	0.062	0.72 (0.51-1.02)	0.065
GG	57 (22.27)	120 (22.64)		0.81 (0.54-1.22)	0.309	0.80 (0.53-1.21)	0.290
Additive			0.175	0.88 (0.72-1.08)	0.229	0.88 (0.72-1.08)	0.215
Dominant	165 (64.45)	375 (70.75)	0.076	0.75 (0.55-1.03)	0.075	0.75 (0.55-1.03)	0.074
Recessive	199 (77.73)	410 (77.36)	0.906	0.98 (0.68-1.40)	0.906	0.97 (0.68-1.39)	0.860
Combined							
CC	135 (36.10)	238 (29.35)		1.00		1.00	
CG	166 (44.39)	404 (49.82)		**0.72 (0.55-0.96)**	**0.023**	**0.73 (0.55-0.96)**	**0.023**
GG	73 (19.52)	169 (20.84)		0.76 (0.54-1.08)	0.123	0.76 (0.54-1.08)	0.123
Additive			0.064	0.85 (0.72-1.01)	0.070	0.85 (0.72-1.01)	0.070
Dominant	239 (63.90)	573 (70.65)	0.020	**0.74 (0.57-0.95)**	**0.020**	**0.74 (0.57-0.95)**	**0.020**
Recessive	303 (80.48)	642 (79.16)	0.600	0.92 (0.68-1.25)	0.601	0.92 (0.68-1.25)	0.596

[a] χ^2 test for genotype distributions between neuroblastoma cases and cancer-free controls

[b] Adjusted for age and gender

Table 2. Stratification analysis for the association between *TP53* rs1042522 C>G polymorphism and neuroblastoma susceptibility

Variables	CC	CG/GG	Crude OR	P	Adjusted OR [a]	P [a]
	(Cases/Controls)		(95% CI)		(95% CI)	
Age, month						
≤18	41/88	83/217	0.82 (0.52-1.29)	0.389	0.82 (0.52-1.29)	0.387
>18	94/150	156/356	**0.70 (0.51-0.96)**	**0.028**	**0.70 (0.51-0.96)**	**0.027**
Gender						
Females	50/99	107/242	0.88 (0.58-1.32)	0.524	0.88 (0.58-1.32)	0.537
Males	85/139	132/331	**0.65 (0.47-0.91)**	**0.013**	**0.66 (0.47-0.92)**	**0.014**
Sites of origin						
Adrenal gland	47/238	88/573	0.78 (0.53-1.14)	0.201	0.78 (0.53-1.15)	0.204
Retroperitoneal	29/238	58/573	0.83 (0.52-1.33)	0.440	0.84 (0.52-1.35)	0.468
Mediastinum	46/238	63/573	**0.57 (0.38-0.86)**	**0.007**	**0.57 (0.38-0.86)**	**0.007**
Others	11/238	24/573	0.91 (0.44-1.88)	0.791	0.91 (0.44-1.89)	0.798
Clinical stages						
I+II+4s	59/238	106/573	0.75 (0.53-1.06)	0.104	0.75 (0.53-1.06)	0.105
III+IV	68/238	121/573	0.74 (0.53-1.03)	0.075	0.74 (0.53-1.04)	0.079

[a] Adjusted for age and gender, omitting the corresponding stratification factor.

Discussion

Compared with the previous study, in this study, we increased the number of samples and conducted a two-centre case-control study in North and South China. In this study, we observed that the *TP53* gene rs1042522 allele G was associated with reduced risk of neuroblastoma. In contrast to the previous study, which found that the *TP53* gene rs1042522 C>G polymorphism was associated with a decreased risk of neuroblastoma in children in South China that was not statistically significant [18], in this study we collected data from children in representative hospitals in both North and South China, so we believe this result has reference value. To the best of our knowledge, this was the largest study in China of the *TP53* gene rs1042522 C>G polymorphism and neuroblastoma risk.

Some studies have shown that genetic variations of tumour suppressor genes or oncogenes can alter the functions of those genes and may contribute to the development of cancer [11]. TP53 has many anticancer functions and plays a crucial role in apoptosis, genomic stability and the inhibition of angiogenesis. The C to G transversion in codon 72 of the *TP53* gene has been associated with increased susceptibility to multiple types of cancers. This polymorphism has been shown to impair TP53 activity, including DNA repair, apoptosis, and cycle arrest [21]. Specifically, *TP53* harbouring the wild-type codon 72 showed an increased ability to transactivate p21 and to induce stagnation of growth compared to variants, which may be a key step in DNA damage repair [22]. Mutations in *TP53* can produce different isoforms that prevent them from having different mechanistic functions in different cells, thereby changing the cancer phenotype from mild to severe [23].

Although growing studies were accessible regarding *TP53* gene rs1042522 C>G polymorphism and the risk of cancers, only two of them focus on neuroblastoma. Cattelani et al. released the first report on *TP53* gene rs1042522 C>G polymorphism on neuroblastoma risk. They failed to detect significant relationship between the *TP53* gene rs1042522 C>G polymorphism and the risk of neuroblastoma in 288 healthy subjects and 286 neuroblastoma patients of European descent [24]. In a three independent case-control cohorts comprising 10290 individuals conducted by Diskin et al., they demonstrated that *TP53* rs78378222 and rs35850753 confer to increase risk of neuroblastoma. However, they were unable to observe any association between the *TP53* gene rs1042522 C>G variant and overall survival in 1,809 neuroblastoma patients [25].

In this study, we analysed the patient's gender, age, primary sites of tumour origin, and the clinical stage of disease and found that the *TP53* gene reduces the risk of developing neuroblastoma in male patients older than 18 months with tumour of mediastinal origins. The role of rs1042522 G allele on the neuroblastoma risk was different from other studies. There are several potential explanations for such conflicting results. First, the same polymorphism might have different role in cancer risk, depending on different ethnicities, regions, and cancer types. Second, such conflicting role might also be the small sample size of all the studies. Third, other risk factors not analysed in the present study may modify *TP53* gene SNP to exert its effect. Due to the reasons mentioned above, the conclusions obtained from our study should be interpreted with caution when extrapolated to other ethnic groups. The current study only focuses on genetic analysis. Functional analysis of SNPs is warranted to characterize the described associations [26-29], which would illustrate the underlying mechanisms of how theses SNPs modify neuroblastoma susceptibility. Although the prognosis of those low-risk neuroblastomas can be improved by the current clinical treatment, the survival rate of those children with high-risk and recurrent neuroblastoma is still not optimistic. Approximately 50% percent of children with a high-risk disease relapse, and the 5-year survival rate in relapsed cases is only 8% [30]. Therefore, finding an early marker that can predict or screen for neuroblastoma is of great importance.

Individualized treatment based on biomarkers will be a necessary option in future medical therapy [31]. Obviously, we also realized in this study that merely finding the DNA sequence changes in tumour cells is not enough. Additionally, we should understand and predict the pathogenesis of neuroblastoma in a more comprehensive way through the analysis of data from expression profiling, epigenetics, proteomics and host germ cell changes. In this way, we can look for more accurate predictive biomarkers in the future to distinguish between different children with neuroblastoma, so that different children can receive individualized treatment.

In the future, our research will focus on the effects of other common and rare disease susceptibility variants of the identified alleles known to be associated with elevated risk. When a greater number of risk-variant genes are identified, a stronger genetic score can be established in order to better identify and predict patients with neuroblastoma at different sites and stages [32]. We think we should collect more data, including information on environmental factors, in children with neuroblastoma in China because the precision and

accuracy of the allele risk analysis will increase as the samples continue to be repeated and expanded [4]. In our recent series of studies [18, 19], the accuracy of this assumption has been seen.

We plan to increase the number of cases in China and to conduct a large number of prospective cohort studies through a multi-centre collaborative project. A more comprehensive and meticulous analysis of all the susceptible genes we find in neuroblastoma and the ongoing refinement of neuroblastoma markers of susceptibility are promising for families with children with poor prognoses.

Supplementary Material

Supplementary table.
http://www.jcancer.org/v10p0467s1.pdf

Acknowledgements

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Competing Interests

The authors have declared that no competing interest exists.

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